

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Elliott Richelson et al.	Art Unit	: 1633
Serial No.	: 10/799,238	Examiner	: Janet L. Epps Ford
Filed	: March 12, 2004	Conf. No.	: 7520
Title	: USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO ENGENDER A BIOLOGICAL RESPONSE		

Mail Stop Appeal Brief - Patents

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

This Appeal Brief is set out in accordance with 37 C.F.R. § 41.37. The Notice of Appeal was filed on March 13, 2008. A Table of Authorities is provided for the convenience of the Examiner and the members of the Board of Patent Appeals and Interferences.

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: August 19, 2008

Applicant : Elliott Richelson et al.
Serial No. : 10/799,238
Filed : March 12, 2004
Page : 2 of 10

Attorney's Docket No.: 07039-126002

TABLE OF AUTHORITIES

Cases	Page
<i>Genentech, Inc. v. Novo Nordisk, A/S</i> , 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir.1997)	4
<i>In re Wright</i> , 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993)	4

(1) Real Party in Interest

The real party in interest is the Mayo Foundation for Medical Education and Research.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 1-14 have been previously cancelled without prejudice. Claims 15-26 are pending and have been at least twice rejected. The rejection of claims 15-26 are appealed herein.

(4) Status of Amendments

All previously presented amendments have been entered.

(5) Summary of Claimed Subject Matter

The claimed subject matter relates to the use of a polyamide nucleic acid oligomer to engender, in a mammal, a biological response in a sequence specific manner. In general, the backbone linkages of the polyamide nucleic acid oligomer can be neutral amide backbone linkages, and the polyamide nucleic acid oligomer can contain a sequence complementary to a target nucleic acid present in the mammal. See, e.g., Applicants' specification at page 15, lines 3-20.

One independent claim is involved in this appeal, claim 15. Claim 15 recites a method of treating cells present in a mammal, said method comprising administering to said cells a polyamide nucleic acid oligomer under conditions wherein said polyamide nucleic acid oligomer engenders a biological response in a sequence specific manner, wherein the backbone linkages of said polyamide nucleic acid oligomer are neutral amide backbone linkages, wherein said polyamide nucleic acid oligomer contains a sequence complementary to a target nucleic acid present in said mammal, wherein said biological response is associated with said target nucleic acid, and wherein said administration is an extracranial administration.

(6) Grounds of Rejection to be Reviewed on Appeal

The Examiner rejected claims 15-26 under 35 U.S.C. § 112, first paragraph, alleging that because the specification, while being enabling for reducing the expression of a target nucleic acid by delivering a polyamide nucleic acid oligomer having a neutral amide backbone and having a sequence complementary to the target nucleic acid, does not reasonably provide enablement for amelioration of any and all disease conditions in any mammal where the overexpression of the target nucleic acid is associated with the disease condition.

(7) Argument

A. Grouping of Claims

For the outstanding rejection alleging that the claims lack enablement for the Examiner's explained reasons, claims 15-26 stand or fall together. This grouping only applies to the outstanding rejection articulated by the Examiner, and other groupings may exist in the event of other rejections or other explanations of a lack of enablement.

B. Arguments for Reversal of Examiner's Rejection

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir.1997) (quoting from *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement...Marzocchi, 439 F.2d at 223-24." *In re Wright*, 999 F.2d at 1561-62.

The first step in an enablement analysis is claim interpretation because it is the language of the claims that determines their scope. In this case, the Examiner contends that the claims are to a "treatment of any disease associated with a target nucleic acid." See, e.g., Advisory Action mailed March 3, 2008.

We do not agree with the Examiner's characterization of the claims vis-à-vis enablement. Claim 15 recites administering to the cells a polyamide nucleic acid oligomer under conditions wherein the polyamide nucleic acid oligomer engenders a biological response in a sequence specific manner. A "biological response" would be understood by persons of skill in the art to include reducing the expression of a target nucleic acid. See, e.g., page 15, lines 3-16 of Applicants' specification.

There is no language in claim 15, or in any of the dependent claims, that states that the engendered biological response must be effective to treat "any disease associated with a target nucleic acid," as the Examiner appears to contend. Thus, any biological response engendered via the polyamide nucleic acid oligomer that is in a sequence specific manner would meet the claimed limitation of a "biological response," including reducing the expression of a target nucleic acid. While Applicants' specification discloses using polyamide nucleic acid oligomers to treat diseases (see, e.g., Applicants' specification at page 27, lines 1-3), the presently pending claims are not limited to this use. For example, the claims require administering a polyamide nucleic acid oligomer under conditions wherein the polyamide nucleic acid oligomer engenders a biological response in a sequence specific manner, whether or not the engendered biological response results in treating a disease. For this reason alone, the Examiner's rejection should be reversed.

Applicants note that, as the Examiner appears to acknowledge, it is clear from the record of the present application, the records of U.S. Patent Application Nos. 09/168,791 (now, U.S. Patent No. 6,723,560), 08/953,269 (now, U.S. Patent No. 6,472,209), and 09/016,685 (now, U.S. Patent No. 6,743,627), and the declarations filed during prosecution of U.S. Patent Application Nos. 09/168,791 (Exhibit A), 08/953,269 (Exhibit B), and 09/016,685 (Exhibit C) that no undue experimentation is needed to administer a polyamide nucleic acid as recited in the pending claims to engender a biological response in a sequence specific manner. Thus, Applicants' specification fully enables the presently pending claims.

Consideration of the above and the record as a whole strongly supports a finding that Applicants' specification enables claims 15-26. Thus, Applicants respectfully request reversal of the Examiner's rejection of claims 15-26 under 35 U.S.C. § 112, first paragraph.

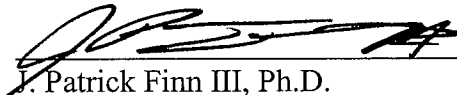
Applicant : Elliott Richelson et al.
Serial No. : 10/799,238
Filed : March 12, 2004
Page : 6 of 10

Attorney's Docket No.: 07039-126002

The brief fee of \$255 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: August 19, 2008


J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (877) 769-7945

60513314.doc

Appendix of Claims

15. A method of treating cells present in a mammal, said method comprising administering to said cells a polyamide nucleic acid oligomer under conditions wherein said polyamide nucleic acid oligomer engenders a biological response in a sequence specific manner, wherein the backbone linkages of said polyamide nucleic acid oligomer are neutral amide backbone linkages, wherein said polyamide nucleic acid oligomer contains a sequence complementary to a target nucleic acid present in said mammal, wherein said biological response is associated with said target nucleic acid, and wherein said administration is an extracranial administration.

16. The method of claim 15, wherein said biological response is characterized by a physiological change in said mammal.

17. The method of claim 15, wherein said method further comprises detecting said biological response.

18. The method of claim 15, wherein said target sequence comprises at least a portion of a coding strand of DNA within said cell, wherein said portion regulates, or is a template for, synthesis of an RNA molecule.

19. The method of claim 18, wherein said RNA molecule encodes a polypeptide.

20. The method of claim 15, wherein said target sequence comprises RNA that regulates expression of or encodes a polypeptide.

21. The method of claim 15, wherein said biological response is a modification of polypeptide expression.

22. The method of claim 21, wherein said modification is a reduction in polypeptide expression.

23. The method of claim 15, wherein said oligomer is carrier-free.
24. The method of claim 15, wherein said oligomer crosses a blood-brain barrier of said mammal.
25. The method of claim 15, wherein said extracranial administration is an intraperitoneal administration.
26. The method of claim 15, wherein said cell is a nervous system cell.

Applicant : Elliott Richelson et al.
Serial No. : 10/799,238
Filed : March 12, 2004
Page : 9 of 10

Attorney's Docket No.: 07039-126002

Evidence Appendix

Copies of each Exhibit listed in the following table are attached hereto.

Exhibit	Document	Date Entered
A	Dr. Richelson's declaration from U.S. Patent Application No. 09/168,791	Implicitly entered by Examiner in Final Office Action of November 13, 2007
B	Dr. Richelson's declarations from U.S. Patent Application No. 08/953,269	Implicitly entered by Examiner in Final Office Action of November 13, 2007
C	Dr. Richelson's declarations from U.S. Patent Application No. 09/016,685	Implicitly entered by Examiner in Final Office Action of November 13, 2007

Applicant : Elliott Richelson et al.
Serial No. : 10/799,238
Filed : March 12, 2004
Page : 10 of 10

Attorney's Docket No.: 07039-126002

Related Proceedings Appendix

None.

EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al. Art Unit: 1635
Serial No.: 09/168,791 Examiner: J. Epps
Filed : October 8, 1998
Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO
ENGENDER A BIOLOGICAL RESPONSE

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.
5. I have read the Examiner's Office Action mailed June 13, 2000.
6. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* screening to identify neurotensin-1 receptor-specific PNA oligomers having *in vivo* activity prior to administering the NTR1-PNA oligomer to a mammal. The NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a

mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the NTR1-PNA oligomer. In addition, neither I, my co-inventors, nor individuals under our supervision have established a cell culture screening method capable of identifying neurotensin-1 receptor-specific PNA oligomers having biological activity.

7. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify mu-1 morphine receptor-specific PNA oligomers having *in vivo* activity prior to administering the MU1R-PNA oligomer to a mammal. The MU1R-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat mu-1 morphine receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the MU1R-PNA oligomer.

8. In a related patent application having serial number 08/953,269, I understand that the Examiner indicated that the experiment identical to the experiment presented in Example 3 of above-indicated patent application should be repeated using a PNA control. Individuals under my supervision conducted experiments using the SERT PNA described in Example 3 of the above-indicated patent application and a control PNA oligomer. The control PNA oligomer had a scrambled sequence with respect to that of the SERT PNA. No statistically significant difference between SERT PNA-treated animals and control PNA-treated animals was detected when behavioral activity was measured. In addition, no statistically significant difference between the levels of serotonin transporter protein measured in the SERT PNA-treated animals and control PNA-treated animals was detected.

9. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat dopamine transporter-specific PNA oligomers having *in vivo* activity prior to administering the antisense DAT-PNA oligomer described in the DAT manuscript (a scientific manuscript submitted for publication entitled

"Altering behavioral responses and dopamine transporter protein with antisense peptide nucleic acids") to a mammal. The antisense DAT-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine transporter that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the DAT manuscript, a sequence specific biological response was detected after *in vivo* administration of the antisense DAT-PNA oligomer.

10. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat angiotensinogen-specific PNA oligomers having *in vivo* activity prior to administering the sense-angiotensinogen PNA oligomer described in the angiotensinogen manuscript (a scientific manuscript submitted for publication entitled "Peptide nucleic acids specifically cause antigene effects *in vivo* by systemic injection") to a mammal. The sense-angiotensinogen PNA oligomer was the first PNA oligomer targeting the coding strand of rat angiotensinogen that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the angiotensinogen manuscript, a sequence specific biological response was detected after *in vivo* administration of the sense-angiotensinogen PNA oligomer.

11. Individuals under my supervision conducted two experiments using a PNA oligomer targeting the coding strand of rat dopamine D2 receptor (sense DOP-PNA). In each experiment, animals treated with the sense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The level of dopamine D2 receptor protein was measured in each experiment. In one experiment, animals treated with the sense DOP-PNA exhibited a significant reduction in the level of dopamine D2 receptor protein measured. In the other experiment, no statistically significant difference was detected in the levels of dopamine D2 receptor protein measured. In a separate experiment, a PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor (antisense DOP-PNA) was administered to animals. In that experiment, animals treated with antisense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The levels of dopamine D2 receptor protein were not measured in this experiment. The sense DOP-PNA oligomer was the first PNA oligomer targeting the coding strand of rat

dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense DOP-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify dopamine D2 receptor-specific PNA oligomers having *in vivo* activity prior to administering the sense DOP-PNA and antisense DOP-PNA oligomers to a mammal.

12. Individuals under my supervision conducted experiments using a PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA) and a control PNA oligomer similar to the sense β -APP-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch β -APP-PNA). The levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured in three experiments. In one of the three experiments, no statistically significant difference was detected between the levels of $A\beta(1-42)$ protein measured in sense β -APP-PNA-treated animals and mismatch β -APP-PNA-treated animals. In the other two experiments, however, animals treated with the sense β -APP-PNA exhibited a significantly lower level of $A\beta(1-42)$ protein when compared to the level exhibited in animals treated with the mismatch β -APP-PNA. In all three experiments, no difference was detected between the levels of $A\beta(1-40)$ protein measured for the two treatment groups. It is noted that a PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA) was administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using the antisense β -APP-PNA. It also is noted that a second PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA2) and a second PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA2) were administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using sense β -APP-PNA2 or antisense β -APP-PNA2. The sense β -APP-PNA and sense β -APP-PNA2 oligomers were the first two PNA oligomers

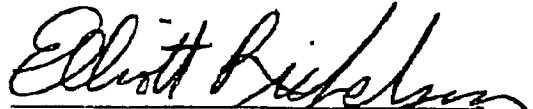
targeting the coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense β -APP-PNA and antisense β -APP-PNA2 oligomers were the first two PNA oligomers targeting the non-coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat β -amyloid precursor protein-specific PNA oligomers having *in vivo* activity prior to administering the antisense β -APP-PNA, antisense β -APP-PNA2, sense β -APP-PNA, and sense β -APP-PNA2 oligomers to a mammal.

13. Individuals under my supervision conducted one experiment using a PNA oligomer targeting the coding strand of the protein component of human telomerase (sense TEL-PNA), a control PNA oligomer similar to sense TEL-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch TEL-PNA), and the PNA oligomer designated MU1R-PNA in the above-identified patent application. In this experiment, animals treated with the sense TEL-PNA exhibited significantly less tumor growth than animals treated with either the mismatch TEL-PNA or the MU1R-PNA. In a separate experiment, tumors from animals treated with the sense TEL-PNA exhibited a significantly lower level of telomerase activity when compared to the level measured in tumors from animals treated with saline. Telomerase activity experiments were not performed using the mismatch TEL-PNA or MU1R-PNA controls. The sense TEL-PNA oligomer was the first PNA oligomer targeting the coding strand of the protein component of human telomerase that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify human telomerase, protein component-specific PNA oligomers having *in vivo* activity prior to administering the sense TEL-PNA oligomer to a mammal.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title

18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 12-12-2000


Elliott Richelson

60027735.doc

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al. Art Unit: 1635
Serial No.: 08/953,269 Examiner: S. McGarry
Filed : October 17, 1997
Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO
ENGENDER A BIOLOGICAL RESPONSE

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.
5. I signed a Declaration that was submitted to the Patent and Trademark Office on October 26, 2000.
6. While preparing a Declaration for a related case having serial number 09/168,714, a review of the notebooks from my laboratory revealed several inadvertent errors in Paragraph 12 of the Declaration submitted October 26, 2000.

7. Paragraph 9 below is a corrected version of Paragraph 12 of the Declaration submitted October 26, 2000. Thus, Paragraph 9 below should be read in place of Paragraph 12 of the Declaration submitted October 26, 2000.

8. Paragraph 10 below is a description of additional experiments related to the experiments described in Paragraph 9 below.

9. Individuals under my supervision conducted experiments using a PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA) and either a saline control or a control PNA oligomer similar to the sense β -APP-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch β -APP-PNA). The levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured in three experiments. In one of the three experiments, the levels of $A\beta(1-42)$ protein were measured in sense β -APP-PNA-treated animals and saline-treated controls with no statistically significant difference being detected. In the other two experiments, however, animals treated with the sense β -APP-PNA exhibited a significantly lower level of $A\beta(1-42)$ protein when compared to the level exhibited for controls (the control for one experiment was saline-treated animals, and the controls for the other experiment were saline-treated animals and mismatch β -APP-PNA-treated animals). In all three experiments, no difference was detected between the levels of $A\beta(1-40)$ protein measured for the sense β -APP-PNA-treated animals and control animals. It is noted that a PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA) was administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected. It also is noted that a second PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA2) and a second PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA2) were administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and compared to the levels measured in animals treated with saline or a control PNA oligomer (mismatch β -APP-PNA2) similar to the sense β -APP-PNA2 with the

exception that it contained a mismatch at every third nucleotide position. No statistically significant difference was detected.

10. The following experiments were conducted in mice. The levels of mouse A β (1-40) and A β (1-42) protein were measured in blood and brain samples collected at different time points (4, 8, 12, 16, and 24 hours post-injection) from mice treated with a single intraperitoneal injection of the sense β -APP-PNA referenced above. These levels were compared to the levels measured in mice treated with saline or the mismatch β -APP-PNA referenced above. No statistically significant difference was detected between the sense β -APP-PNA-treated mice and control mice when the plasma levels of mouse A β (1-40) and A β (1-42) protein were measured. Mice treated with the sense β -APP-PNA did exhibit a significantly lower level of A β (1-40) and A β (1-42) protein in their brains at the 16 hour post-injection time point when compared to the brain levels exhibited for control mice. In addition, mice were treated with a single intraperitoneal injection containing one of the following nine PNA oligomers: three PNA oligomers targeting the coding strand of mouse β -amyloid precursor protein, one PNA oligomer targeting the non-coding strand of mouse β -amyloid precursor protein, three PNA oligomers targeting the coding strand of mouse beta-amyloid cleaving enzyme (BACE), and two PNA oligomers targeting the non-coding strand of mouse BACE. Control mice were treated with either the mismatch β -APP-PNA or saline. Seven of the PNA oligomers targeting either mouse β -amyloid precursor protein or mouse BACE that were administered to mice resulted in no difference in plasma A β (1-40) or A β (1-42) protein levels when compared to the levels measured in either the mismatch β -APP-PNA-treated mice or saline-treated mice. One sense PNA oligomer targeting mouse β -amyloid precursor protein (sense -47APP-PNA) resulted in a 21 percent decrease in plasma A β (1-40) protein levels ($p < 0.15$), while one antisense PNA oligomer targeting mouse BACE (antisense +29BACE PNA) resulted in a 25 percent decrease in plasma A β (1-40) protein levels ($p < 0.13$). In another experiment, mice were injected with four daily injections of either the sense β -APP-PNA, the sense -47APP-PNA, the antisense +29BACE PNA, or saline. The sense β -APP-PNA-treated mice and antisense +29BACE PNA-treated mice exhibited plasma A β (1-40) protein levels comparable to those measured in saline-treated mice. The sense -47APP-PNA-

treated mice, however, exhibited a 31 percent decrease in plasma A β (1-42) protein levels when compared to saline-treated mice ($p < 0.06$). In another experiment, mice were intraperitoneally injected with the sense -47APP-PNA or saline control either daily for four days, twice daily for four days, or daily for 12 days. No change in brain A β (1-40) or A β (1-42) protein levels or mRNA levels was observed between the sense -47APP-PNA-treated mice and saline-treated control mice. In addition, the sense -47APP-PNA was not detected in the brain samples collected from the sense -47APP-PNA-treated mice. PNA oligomers (six total including the sense -47APP-PNA) were also not detected in brain samples collected from mice having had received a single intraperitoneal injection. The sense β -APP-PNA, however, was detected in brain samples collected from mice treated intraperitoneally with the sense β -APP-PNA daily for four days.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 12/31/2001


Elliott Richelson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al. Art Unit: 1635
Serial No.: 08/953,269 Examiner: S. McGarry
Filed : October 17, 1997
Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO
ENGENDER A BIOLOGICAL RESPONSE

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.
5. I signed a Declaration that was submitted to the Patent and Trademark Office on October 26, 2000.
6. While preparing a Declaration for a related case having serial number 09/168,714, a review of the notebooks from my laboratory revealed several inadvertent errors in Paragraph 12 of the Declaration submitted October 26, 2000.

7. Paragraph 9 below is a corrected version of Paragraph 12 of the Declaration submitted October 26, 2000. Thus, Paragraph 9 below should be read in place of Paragraph 12 of the Declaration submitted October 26, 2000.

8. Paragraph 10 below is a description of additional experiments related to the experiments described in Paragraph 9 below.

9. Individuals under my supervision conducted experiments using a PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA) and either a saline control or a control PNA oligomer similar to the sense β -APP-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch β -APP-PNA). The levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured in three experiments. In one of the three experiments, the levels of $A\beta(1-42)$ protein were measured in sense β -APP-PNA-treated animals and saline-treated controls with no statistically significant difference being detected. In the other two experiments, however, animals treated with the sense β -APP-PNA exhibited a significantly lower level of $A\beta(1-42)$ protein when compared to the level exhibited for controls (the control for one experiment was saline-treated animals, and the controls for the other experiment were saline-treated animals and mismatch β -APP-PNA-treated animals). In all three experiments, no difference was detected between the levels of $A\beta(1-40)$ protein measured for the sense β -APP-PNA-treated animals and control animals. It is noted that a PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA) was administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected. It also is noted that a second PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA2) and a second PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA2) were administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and compared to the levels measured in animals treated with saline or a control PNA oligomer (mismatch β -APP-PNA2) similar to the sense β -APP-PNA2 with the


exception that it contained a mismatch at every third nucleotide position. No statistically significant difference was detected.

10. The following experiments were conducted in mice. The levels of mouse A β (1-40) and A β (1-42) protein were measured in blood and brain samples collected at different time points (4, 8, 12, 16, and 24 hours post-injection) from mice treated with a single intraperitoneal injection of the sense β -APP-PNA referenced above. These levels were compared to the levels measured in mice treated with saline or the mismatch β -APP-PNA referenced above. No statistically significant difference was detected between the sense β -APP-PNA-treated mice and control mice when the plasma levels of mouse A β (1-40) and A β (1-42) protein were measured. Mice treated with the sense β -APP-PNA did exhibit a significantly lower level of A β (1-40) and A β (1-42) protein in their brains at the 16 hour post-injection time point when compared to the brain levels exhibited for control mice. In addition, mice were treated with a single intraperitoneal injection containing one of the following nine PNA oligomers: three PNA oligomers targeting the coding strand of mouse β -amyloid precursor protein, one PNA oligomer targeting the non-coding strand of mouse β -amyloid precursor protein, three PNA oligomers targeting the coding strand of mouse beta-amyloid cleaving enzyme (BACE), and two PNA oligomers targeting the non-coding strand of mouse BACE. Control mice were treated with either the mismatch β -APP-PNA or saline. Seven of the PNA oligomers targeting either mouse β -amyloid precursor protein or mouse BACE that were administered to mice resulted in no difference in plasma A β (1-40) or A β (1-42) protein levels when compared to the levels measured in either the mismatch β -APP-PNA-treated mice or saline-treated mice. One sense PNA oligomer targeting mouse β -amyloid precursor protein (sense -47APP-PNA) resulted in a 21 percent decrease in plasma A β (1-40) protein levels ($p < 0.15$), while one antisense PNA oligomer targeting mouse BACE (antisense +29BACE PNA) resulted in a 25 percent decrease in plasma A β (1-40) protein levels ($p < 0.13$). In another experiment, mice were injected with four daily injections of either the sense β -APP-PNA, the sense -47APP-PNA, the antisense +29BACE PNA, or saline. The sense β -APP-PNA-treated mice and antisense +29BACE PNA-treated mice exhibited plasma A β (1-40) protein levels comparable to those measured in saline-treated mice. The sense -47APP-PNA-

treated mice, however, exhibited a 31 percent decrease in plasma A β (1-42) protein levels when compared to saline-treated mice ($p < 0.06$). In another experiment, mice were intraperitoneally injected with the sense -47APP-PNA or saline control either daily for four days, twice daily for four days, or daily for 12 days. No change in brain A β (1-40) or A β (1-42) protein levels or mRNA levels was observed between the sense -47APP-PNA-treated mice and saline-treated control mice. In addition, the sense -47APP-PNA was not detected in the brain samples collected from the sense -47APP-PNA-treated mice. PNA oligomers (six total including the sense -47APP-PNA) were also not detected in brain samples collected from mice having had received a single intraperitoneal injection. The sense β -APP-PNA, however, was detected in brain samples collected from mice treated intraperitoneally with the sense β -APP-PNA daily for four days.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 12/31/2001


Elliott Richelson

PATENT
ATTORNEY DOCKET NO. 07039/073001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al.

Art Unit: 1635

Serial No.: 08/953,269

Examiner: Sean McGarry

Filed : October 17, 1997

Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO
ENGENDER A BIOLOGICAL RESPONSE

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

October 26, 2000

Date of Deposit

Signature



Jill Hyse

Typed or Printed Name of Person Signing Certificate

5. I have read the Examiner's Office Actions mailed September 13, 1999 and April 26, 2000, including the sections where the Examiner contends that neither the specification nor my previous Declaration provides any guidance or evidence of how the PNA oligomers were initially screened for their expected *in vivo* activity.
6. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* screening to identify neurotensin-1 receptor-specific PNA oligomers having *in vivo* activity prior to administering the NTR1-PNA oligomer to a mammal. The NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the NTR1-PNA oligomer. In addition, neither I, my co-inventors, nor individuals under our supervision have established a cell culture screening method capable of identifying neurotensin-1 receptor-specific PNA oligomers having biological activity.
7. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify mu-1 morphine receptor-specific PNA oligomers having *in vivo* activity prior to administering the MU1R-PNA oligomer to a mammal. The MU1R-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat mu-1 morphine receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the MU1R-PNA oligomer.
8. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat dopamine transporter-specific PNA oligomers having *in vivo* activity prior to administering the antisense DAT-PNA oligomer described in the DAT manuscript (a scientific manuscript submitted for publication entitled "Altering behavioral responses and dopamine transporter protein with antisense peptide nucleic acids") to a mammal. The antisense DAT-PNA oligomer was the first PNA

110.211 P. 47

oligomer targeting the non-coding strand of rat dopamine transporter that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the DAT manuscript, a sequence specific biological response was detected after *in vivo* administration of the antisense DAT-PNA oligomer.

9. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat angiotensinogen-specific PNA oligomers having *in vivo* activity prior to administering the sense-angiotensinogen PNA oligomer described in the angiotensinogen manuscript (a scientific manuscript submitted for publication entitled "Peptide nucleic acids specifically cause antigene effects *in vivo* by systemic injection") to a mammal. The sense-angiotensinogen PNA oligomer was the first PNA oligomer targeting the coding strand of rat angiotensinogen that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the angiotensinogen manuscript, a sequence specific biological response was detected after *in vivo* administration of the sense-angiotensinogen PNA oligomer.

10. I understand that the Examiner, during a telephonic interview with Patrick Finn on March 16, 2000, indicated that the experiment presented in Example 3 of WO 99/20643 should be repeated using a PNA control. Individuals under my supervision conducted experiments using the SERT PNA described in Example 3 of WO 99/20643 and a control PNA oligomer. The control PNA oligomer had a scrambled sequence with respect to that of the SERT PNA. No statistically significant difference between SERT PNA-treated animals and control PNA-treated animals was detected when behavioral activity was measured. In addition, no statistically significant difference between the levels of serotonin transporter protein measured in the SERT PNA-treated animals and control PNA-treated animals was detected.

11. Individuals under my supervision conducted two experiments using a PNA oligomer targeting the coding strand of rat dopamine D2 receptor (sense DOP-PNA). In each experiment, animals treated with the sense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The level of dopamine D2 receptor protein

was measured in each experiment. In one experiment, animals treated with the sense DOP-PNA exhibited a significant reduction in the level of dopamine D2 receptor protein measured. In the other experiment, no statistically significant difference was detected in the levels of dopamine D2 receptor protein measured. In a separate experiment, a PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor (antisense DOP-PNA) was administered to animals. In that experiment, animals treated with antisense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The levels of dopamine D2 receptor protein were not measured in this experiment. The sense DOP-PNA oligomer was the first PNA oligomer targeting the coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense DOP-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify dopamine D2 receptor-specific PNA oligomers having *in vivo* activity prior to administering the sense DOP-PNA and antisense DOP-PNA oligomers to a mammal.

12. Individuals under my supervision conducted experiments using a PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA) and a control PNA oligomer similar to the sense β -APP-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch β -APP-PNA). The levels of A β (1-40) and A β (1-42) protein were measured in three experiments. In one of the three experiments, no statistically significant difference was detected between the levels of A β (1-42) protein measured in sense β -APP-PNA-treated animals and mismatch β -APP-PNA-treated animals. In the other two experiments, however, animals treated with the sense β -APP-PNA exhibited a significantly lower level of A β (1-42) protein when compared to the level exhibited in animals treated with the mismatch β -APP-PNA. In all three experiments, no difference was detected between the levels of A β (1-40) protein measured for the two treatment groups. It is noted that a PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA) was

administered to animals. After administration, the levels of A β (1-40) and A β (1-42) protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using the antisense β -APP-PNA. It also is noted that a second PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA2) and a second PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA2) were administered to animals. After administration, the levels of A β (1-40) and A β (1-42) protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using sense β -APP-PNA2 or antisense β -APP-PNA2. The sense β -APP-PNA and sense β -APP-PNA2 oligomers were the first two PNA oligomers targeting the coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense β -APP-PNA and antisense β -APP-PNA2 oligomers were the first two PNA oligomers targeting the non-coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat β -amyloid precursor protein-specific PNA oligomers having *in vivo* activity prior to administering the antisense β -APP-PNA, antisense β -APP-PNA2, sense β -APP-PNA, and sense β -APP-PNA2 oligomers to a mammal.

13. Individuals under my supervision conducted one experiment using a PNA oligomer targeting the coding strand of the protein component of human telomerase (sense TEL-PNA), a control PNA oligomer similar to sense TEL-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch TEL-PNA), and the PNA oligomer designated MU1R-PNA in the above-identified patent application. In this experiment, animals treated with the sense TEL-PNA exhibited significantly less tumor growth than animals treated with either the mismatch TEL-PNA or the MU1R-PNA. In a separate experiment, tumors from animals treated with the sense TEL-PNA

exhibited a significantly lower level of telomerase activity when compared to the level measured in tumors from animals treated with saline. Telomerase activity experiments were not performed using the mismatch TEL-PNA or MU1R-PNA controls. The sense TEL-PNA oligomer was the first PNA oligomer targeting the coding strand of the protein component of human telomerase that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify human telomerase, protein component-specific PNA oligomers having *in vivo* activity prior to administering the sense TEL-PNA oligomer to a mammal.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 10/26/2000

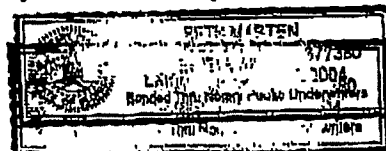
Elliott Richelson
Elliott Richelson

STATE OF FLORIDA)
COUNTY OF Duval) ss.

Before me this 26th day of October, 2000, personally appeared Elliott Richelson known to me to be the person whose name is subscribed to the foregoing Declaration, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Beth Marten
Notary Public

60024884.doc



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al. Art Unit: 1635
Serial No.: 08/953,269 Examiner: Sean McGarry
Filed : October 17, 1997
Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO
 ENGENDER A BIOLOGICAL RESPONSE

Assistant Commissioner for Patents
Washington, DC 20231
BOX AF

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

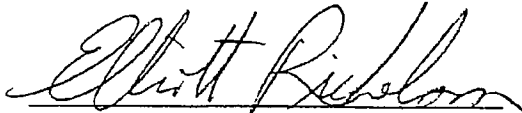
1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.
5. I have read the Examiner's Office Action mailed September 13, 1999, including the section where the Examiner contends that neither the specification nor my previous Declaration provides any guidance or evidence of how the PNA oligomers were initially screened for their expected *in vivo* activity.
6. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* screening to identify neurotensin-1 receptor-specific PNA oligomers having *in vivo*

activity prior to administering the NTR1-PNA oligomer to a mammal. The NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the NTR1-PNA oligomer. In addition, neither I, my co-inventors, nor individuals under our supervision have established a cell culture screening method capable of identifying neurotensin-1 receptor-specific PNA oligomers having biological activity.

7. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify mu-1 morphine receptor-specific PNA oligomers having *in vivo* activity prior to administering the MU1R-PNA oligomer to a mammal. The MU1R-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat mu-1 morphine receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the MU1R-PNA oligomer.

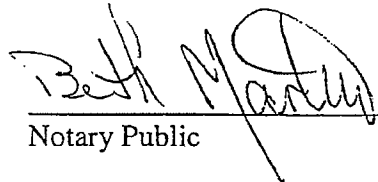
8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 11/12/99


Elliott Richelson

STATE OF FLORIDA)
) ss.
COUNTY OF Duval)

Before me this 12th day of November, 1999, personally appeared Elliott Richelson known to me to be the person whose name is subscribed to the foregoing Declaration, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.



Notary Public

60001604.doc



PATENT
ATTORNEY DOCKET NO. 07039/073001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al. Art Unit: 1635
Serial No.: 08/953,269 Examiner: Sean McGarry
Filed : October 17, 1997
Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO
 ENGENDER A BIOLOGICAL RESPONSE

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

October 26, 2000

Date of Deposit

Signature

Jill Hugg
Typed or Printed Name of Person Signing Certificate

5. I have read the Examiner's Office Actions mailed September 13, 1999 and April 26, 2000, including the sections where the Examiner contends that neither the specification nor my previous Declaration provides any guidance or evidence of how the PNA oligomers were initially screened for their expected *in vivo* activity.

6. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* screening to identify neurotensin-1 receptor-specific PNA oligomers having *in vivo* activity prior to administering the NTR1-PNA oligomer to a mammal. The NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the NTR1-PNA oligomer. In addition, neither I, my co-inventors, nor individuals under our supervision have established a cell culture screening method capable of identifying neurotensin-1 receptor-specific PNA oligomers having biological activity.

7. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify mu-1 morphine receptor-specific PNA oligomers having *in vivo* activity prior to administering the MU1R-PNA oligomer to a mammal. The MU1R-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat mu-1 morphine receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the MU1R-PNA oligomer.

8. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat dopamine transporter-specific PNA oligomers having *in vivo* activity prior to administering the antisense DAT-PNA oligomer described in the DAT manuscript (a scientific manuscript submitted for publication entitled "Altering behavioral responses and dopamine transporter protein with antisense peptide nucleic acids") to a mammal. The antisense DAT-PNA oligomer was the first PNA

oligomer targeting the non-coding strand of rat dopamine transporter that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the DAT manuscript, a sequence specific biological response was detected after *in vivo* administration of the antisense DAT-PNA oligomer.

9. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat angiotensinogen-specific PNA oligomers having *in vivo* activity prior to administering the sense-angiotensinogen PNA oligomer described in the angiotensinogen manuscript (a scientific manuscript submitted for publication entitled "Peptide nucleic acids specifically cause antigene effects *in vivo* by systemic injection") to a mammal. The sense-angiotensinogen PNA oligomer was the first PNA oligomer targeting the coding strand of rat angiotensinogen that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the angiotensinogen manuscript, a sequence specific biological response was detected after *in vivo* administration of the sense-angiotensinogen PNA oligomer.

10. I understand that the Examiner, during a telephonic interview with Patrick Finn on March 16, 2000, indicated that the experiment presented in Example 3 of WO 99/20643 should be repeated using a PNA control. Individuals under my supervision conducted experiments using the SERT PNA described in Example 3 of WO 99/20643 and a control PNA oligomer. The control PNA oligomer had a scrambled sequence with respect to that of the SERT PNA. No statistically significant difference between SERT PNA-treated animals and control PNA-treated animals was detected when behavioral activity was measured. In addition, no statistically significant difference between the levels of serotonin transporter protein measured in the SERT PNA-treated animals and control PNA-treated animals was detected.

11. Individuals under my supervision conducted two experiments using a PNA oligomer targeting the coding strand of rat dopamine D2 receptor (sense DOP-PNA). In each experiment, animals treated with the sense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The level of dopamine D2 receptor protein

was measured in each experiment. In one experiment, animals treated with the sense DOP-PNA exhibited a significant reduction in the level of dopamine D2 receptor protein measured. In the other experiment, no statistically significant difference was detected in the levels of dopamine D2 receptor protein measured. In a separate experiment, a PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor (antisense DOP-PNA) was administered to animals. In that experiment, animals treated with antisense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The levels of dopamine D2 receptor protein were not measured in this experiment. The sense DOP-PNA oligomer was the first PNA oligomer targeting the coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense DOP-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify dopamine D2 receptor-specific PNA oligomers having *in vivo* activity prior to administering the sense DOP-PNA and antisense DOP-PNA oligomers to a mammal.

12. Individuals under my supervision conducted experiments using a PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA) and a control PNA oligomer similar to the sense β -APP-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch β -APP-PNA). The levels of A β (1-40) and A β (1-42) protein were measured in three experiments. In one of the three experiments, no statistically significant difference was detected between the levels of A β (1-42) protein measured in sense β -APP-PNA-treated animals and mismatch β -APP-PNA-treated animals. In the other two experiments, however, animals treated with the sense β -APP-PNA exhibited a significantly lower level of A β (1-42) protein when compared to the level exhibited in animals treated with the mismatch β -APP-PNA. In all three experiments, no difference was detected between the levels of A β (1-40) protein measured for the two treatment groups. It is noted that a PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA) was

administered to animals. After administration, the levels of A β (1-40) and A β (1-42) protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using the antisense β -APP-PNA. It also is noted that a second PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA2) and a second PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA2) were administered to animals. After administration, the levels of A β (1-40) and A β (1-42) protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using sense β -APP-PNA2 or antisense β -APP-PNA2. The sense β -APP-PNA and sense β -APP-PNA2 oligomers were the first two PNA oligomers targeting the coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense β -APP-PNA and antisense β -APP-PNA2 oligomers were the first two PNA oligomers targeting the non-coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat β -amyloid precursor protein-specific PNA oligomers having *in vivo* activity prior to administering the antisense β -APP-PNA, antisense β -APP-PNA2, sense β -APP-PNA, and sense β -APP-PNA2 oligomers to a mammal.

13. Individuals under my supervision conducted one experiment using a PNA oligomer targeting the coding strand of the protein component of human telomerase (sense TEL-PNA), a control PNA oligomer similar to sense TEL-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch TEL-PNA), and the PNA oligomer designated MU1R-PNA in the above-identified patent application. In this experiment, animals treated with the sense TEL-PNA exhibited significantly less tumor growth than animals treated with either the mismatch TEL-PNA or the MU1R-PNA. In a separate experiment, tumors from animals treated with the sense TEL-PNA

exhibited a significantly lower level of telomerase activity when compared to the level measured in tumors from animals treated with saline. Telomerase activity experiments were not performed using the mismatch TEL-PNA or MUIR-PNA controls. The sense TEL-PNA oligomer was the first PNA oligomer targeting the coding strand of the protein component of human telomerase that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify human telomerase, protein component-specific PNA oligomers having *in vivo* activity prior to administering the sense TEL-PNA oligomer to a mammal.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 10/26/2000

Elliott Richelson
Elliott Richelson

STATE OF FLORIDA)
) ss.
COUNTY OF Duval)

Before me this 26th day of October, 2000, personally appeared Elliott Richelson known to me to be the person whose name is subscribed to the foregoing Declaration, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Beth Marten
Notary Public

60024884.doc

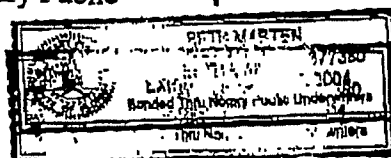


EXHIBIT C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Elliott Richelson et al.

Art Unit: 1635

Serial No.: 09/016,685

Examiner: S. McGarry

Filed : January 30, 1998

Title : USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO
ENGENDER A BIOLOGICAL RESPONSE

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.
5. I have read the Examiner's Office Action mailed July 12, 2000.
6. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* screening to identify neurotensin-1 receptor-specific PNA oligomers having *in vivo* activity prior to administering the NTR1-PNA oligomer to a mammal. The NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the NTR1-PNA oligomer. In addition, neither I, my co-inventors, nor individuals under our supervision have established a cell culture screening method capable of identifying neurotensin-1 receptor-specific PNA oligomers having biological activity.
7. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture

screening to identify mu-1 morphine receptor-specific PNA oligomers having *in vivo* activity prior to administering the MU1R-PNA oligomer to a mammal. The MU1R-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat mu-1 morphine receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after *in vivo* administration of the MU1R-PNA oligomer.

8. In a related patent application having serial number 08/953,269, I understand that the Examiner indicated that the experiment identical to the experiment presented in Example 3 of above-indicated patent application should be repeated using a PNA control. Individuals under my supervision conducted experiments using the SERT PNA described in Example 3 of the above-indicated patent application and a control PNA oligomer. The control PNA oligomer had a scrambled sequence with respect to that of the SERT PNA. No statistically significant difference between SERT PNA-treated animals and control PNA-treated animals was detected when behavioral activity was measured. In addition, no statistically significant difference between the levels of serotonin transporter protein measured in the SERT PNA-treated animals and control PNA-treated animals was detected.

9. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat dopamine transporter-specific PNA oligomers having *in vivo* activity prior to administering the antisense DAT-PNA oligomer described in the DAT manuscript (a scientific manuscript submitted for publication entitled "Altering behavioral responses and dopamine transporter protein with antisense peptide nucleic acids") to a mammal. The antisense DAT-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine transporter that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the DAT manuscript, a sequence specific biological response was detected after *in vivo* administration of the antisense DAT-PNA oligomer.

10. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat angiotensinogen-specific PNA oligomers having *in vivo* activity prior to administering the sense-angiotensinogen PNA oligomer described in the angiotensinogen manuscript (a scientific manuscript submitted for publication entitled "Peptide nucleic acids specifically cause antigene effects *in vivo* by systemic injection") to a mammal. The sense-angiotensinogen PNA oligomer was the first PNA oligomer targeting the coding strand of rat angiotensinogen that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the angiotensinogen manuscript, a sequence specific biological response was detected after *in vivo* administration of the sense-angiotensinogen PNA oligomer.

11. Individuals under my supervision conducted two experiments using a PNA oligomer targeting the coding strand of rat dopamine D2 receptor (sense DOP-PNA). In each experiment, animals treated with the

sense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The level of dopamine D2 receptor protein was measured in each experiment. In one experiment, animals treated with the sense DOP-PNA exhibited a significant reduction in the level of dopamine D2 receptor protein measured. In the other experiment, no statistically significant difference was detected in the levels of dopamine D2 receptor protein measured. In a separate experiment, a PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor (antisense DOP-PNA) was administered to animals. In that experiment, animals treated with antisense DOP-PNA exhibited significantly more catalepsy than animals treated with saline. The levels of dopamine D2 receptor protein were not measured in this experiment. The sense DOP-PNA oligomer was the first PNA oligomer targeting the coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense DOP-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat dopamine D2 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify dopamine D2 receptor-specific PNA oligomers having *in vivo* activity prior to administering the sense DOP-PNA and antisense DOP-PNA oligomers to a mammal.

12. Individuals under my supervision conducted experiments using a PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA) and a control PNA oligomer similar to the sense β -APP-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch β -APP-PNA). The levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured in three experiments. In one of the three experiments, no statistically significant difference was detected between the levels of $A\beta(1-42)$ protein measured in sense β -APP-PNA-treated animals and mismatch β -APP-PNA-treated animals. In the other two experiments, however, animals treated with the sense β -APP-PNA exhibited a significantly lower level of $A\beta(1-42)$ protein when compared to the level exhibited in animals treated with the mismatch β -APP-PNA. In all three experiments, no difference was detected between the levels of $A\beta(1-40)$ protein measured for the two treatment groups. It is noted that a PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA) was administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using the antisense β -APP-PNA. It also is noted that a second PNA oligomer targeting the coding strand of rat β -amyloid precursor protein (sense β -APP-PNA2) and a second PNA oligomer targeting the non-coding strand of rat β -amyloid precursor protein (antisense β -APP-PNA2) were administered to animals. After administration, the levels of $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured and

compared to the levels measured in animals treated with saline. No statistically significant difference was detected, and no further experiments were conducted using sense β -APP-PNA2 or antisense β -APP-PNA2. The sense β -APP-PNA and sense β -APP-PNA2 oligomers were the first two PNA oligomers targeting the coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. The antisense β -APP-PNA and antisense β -APP-PNA2 oligomers were the first two PNA oligomers targeting the non-coding strand of rat β -amyloid precursor protein that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify rat β -amyloid precursor protein-specific PNA oligomers having *in vivo* activity prior to administering the antisense β -APP-PNA, antisense β -APP-PNA2, sense β -APP-PNA, and sense β -APP-PNA2 oligomers to a mammal.

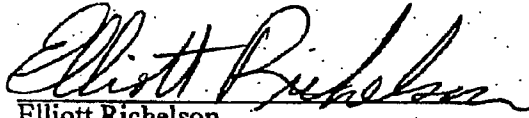
13. Individuals under my supervision conducted one experiment using a PNA oligomer targeting the coding strand of the protein component of human telomerase (sense TEL-PNA), a control PNA oligomer similar to sense TEL-PNA with the exception that it contained a mismatch at every third nucleotide position (mismatch TEL-PNA), and the PNA oligomer designated MU1R-PNA in the above-identified patent application. In this experiment, animals treated with the sense TEL-PNA exhibited significantly less tumor growth than animals treated with either the mismatch TEL-PNA or the MU1R-PNA. In a separate experiment, tumors from animals treated with the sense TEL-PNA exhibited a significantly lower level of telomerase activity when compared to the level measured in tumors from animals treated with saline. Telomerase activity experiments were not performed using the mismatch TEL-PNA or MU1R-PNA controls. The sense TEL-PNA oligomer was the first PNA oligomer targeting the coding strand of the protein component of human telomerase that I, my co-inventors, or individuals under our supervision, administered to a mammal. Neither I, my co-inventors, nor individuals under our supervision performed *in vivo* or cell culture screening to identify human telomerase, protein component-specific PNA oligomers having *in vivo* activity prior to administering the sense TEL-PNA oligomer to a mammal.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize

the validity of the instant patent application or any patent issuing thereon.

Dated: _____

11/11/01


Elliott Richelson

60030330.doc

Jerry Wasiluk

5. That I, my co-inventors, or individuals under our supervision, selected the sequence for the NTR1-PNA oligomer described in the above-indicated patent application. The NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after the *in vivo* administration of the NTR1-PNA oligomer. In addition, the NTR1-PNA oligomer was the first PNA oligomer of any kind that I, my co-inventors, or individuals under our supervision, orally administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after the oral administration of the NTR1-PNA oligomer;

6. That I, my co-inventors, or individuals under our supervision, selected the sequence for the MU1R-PNA oligomer described in the above-indicated patent application. The MU1R-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat mu-1 morphine receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after the *in vivo* administration of the MU1R-PNA oligomer;

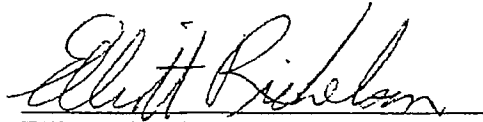
7. That I, my co-inventors, or individuals under our supervision, selected the sequence for the SERT-PNA oligomer described in the above-indicated patent application. The SERT-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat plasma membrane serotonin transporter that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the above-indicated patent application, a sequence specific biological response was detected after the *in vivo* administration of the SERT-PNA oligomer;

8. That I, my co-inventors, or individuals under our supervision, selected the sequence for the sense-NTR1-PNA oligomer described in International Patent Application number PCT/US98/21888 filed October 16, 1998 (WO 99/20643). The sense-NTR1-PNA oligomer was the first PNA oligomer targeting the coding strand of rat neurotensin-1 receptor that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the International Patent Application number PCT/US98/21888, a sequence specific biological response was detected after the *in vivo* administration of the sense-NTR1-PNA oligomer;

9. That I, my co-inventors, or individuals under our supervision, selected the sequence for the mismatch-NTR1-PNA oligomer described in International Patent Application number PCT/US98/21888 filed October 16, 1998 (WO 99/20643). The mismatch-NTR1-PNA oligomer was the first PNA oligomer targeting the non-coding strand of rat neurotensin-1 receptor and containing a mismatch that I, my co-inventors, or individuals under our supervision, administered to a mammal. As described in the International Patent Application number PCT/US98/21888, a sequence specific biological response that was modulated with respect to the responses engendered by the NTR1-PNA oligomer was detected after the *in vivo* administration of the mismatch-NTR1-PNA oligomer;

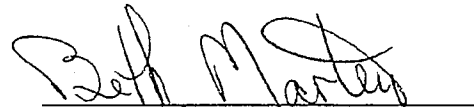
10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 8-6-99


Elliott Richelson

STATE OF FLORIDA)
) ss.
COUNTY OF Duval)

Before me this 6th day of August, 1999, personally appeared Elliott Richelson known to me to be the person whose name is subscribed to the foregoing Declaration, and acknowledged that he executed the same as his free act and deed for the purposes therein contained.


Notary Public

24020.M11



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Elliott Richelson et al.	Art Unit:	1635
Serial No.:	09/016,685	Examiner:	S. McGarry
Filed :	January 30, 1998		
Title :	USING POLYAMIDE NUCLEIC ACID OLIGOMERS TO ENGENDER A BIOLOGICAL RESPONSE		

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR §1.132 OF ELLIOTT RICHELSON

I, Elliott Richelson, declare as follows:

1. I am a citizen of the United States and presently live at 109 Teal Pointe Lane, Ponte Vedra Beach, FL 32082-1936.
2. I am presently employed by Mayo Foundation, and have been so employed since 1975.
3. I received a Doctor of Medicine Degree from Johns Hopkins University, School of Medicine, Baltimore, MD.
4. I am an inventor on the above-indicated patent application.
5. I signed a Declaration that was submitted to the Patent and Trademark Office on January 11, 2001.
6. While preparing a Declaration for a related case having serial number 09/168,714, a review of the notebooks from my laboratory revealed several inadvertent errors in Paragraph 12 of the Declaration submitted January 11, 2001.


PNA oligomer (mismatch β -APP-PNA2) similar to the sense β -APP-PNA2 with the exception that it contained a mismatch at every third nucleotide position. No statistically significant difference was detected.

10. The following experiments were conducted in mice. The levels of mouse $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured in blood and brain samples collected at different time points (4, 8, 12, 16, and 24 hours post-injection) from mice treated with a single intraperitoneal injection of the sense β -APP-PNA referenced above. These levels were compared to the levels measured in mice treated with saline or the mismatch β -APP-PNA referenced above. No statistically significant difference was detected between the sense β -APP-PNA-treated mice and control mice when the plasma levels of mouse $A\beta(1-40)$ and $A\beta(1-42)$ protein were measured. Mice treated with the sense β -APP-PNA did exhibit a significantly lower level of $A\beta(1-40)$ and $A\beta(1-42)$ protein in their brains at the 16 hour post-injection time point when compared to the brain levels exhibited for control mice. In addition, mice were treated with a single intraperitoneal injection containing one of the following nine PNA oligomers: three PNA oligomers targeting the coding strand of mouse β -amyloid precursor protein, one PNA oligomer targeting the non-coding strand of mouse β -amyloid precursor protein, three PNA oligomers targeting the coding strand of mouse beta-amyloid cleaving enzyme (BACE), and two PNA oligomers targeting the non-coding strand of mouse BACE. Control mice were treated with either the mismatch β -APP-PNA or saline. Seven of the PNA oligomers targeting either mouse β -amyloid precursor protein or mouse BACE that were administered to mice resulted in no difference in plasma $A\beta(1-40)$ or $A\beta(1-42)$ protein levels when compared to the levels measured in either the mismatch β -APP-PNA-treated mice or saline-treated mice. One sense PNA oligomer targeting mouse β -amyloid precursor protein (sense -47APP-PNA) resulted in a 21 percent decrease in plasma $A\beta(1-40)$ protein levels ($p < 0.15$), while one antisense PNA oligomer targeting mouse BACE (antisense +29BACE PNA) resulted in a 25 percent decrease in plasma $A\beta(1-40)$ protein levels ($p < 0.13$). In another experiment, mice were injected with four daily injections of either the sense β -APP-PNA, the sense -47APP-PNA, the antisense +29BACE PNA, or saline. The sense β -APP-PNA-treated

mice and antisense +29BACE PNA-treated mice exhibited plasma A β (1-40) protein levels comparable to those measured in saline-treated mice. The sense -47APP-PNA-treated mice, however, exhibited a 31 percent decrease in plasma A β (1-42) protein levels when compared to saline-treated mice ($p < 0.06$). In another experiment, mice were intraperitoneally injected with the sense -47APP-PNA or saline control either daily for four days, twice daily for four days, or daily for 12 days. No change in brain A β (1-40) or A β (1-42) protein levels or mRNA levels was observed between the sense -47APP-PNA-treated mice and saline-treated control mice. In addition, the sense -47APP-PNA was not detected in the brain samples collected from the sense -47APP-PNA-treated mice. PNA oligomers (six total including the sense -47APP-PNA) were also not detected in brain samples collected from mice having had received a single intraperitoneal injection. The sense β -APP-PNA, however, was detected in brain samples collected from mice treated intraperitoneally with the sense β -APP-PNA daily for four days.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Dated: 10-30-2001


Elliott Richelson